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(22) Inventor: Yamabe, Shigeru
1-2-7, Sumiyoshi-kamokohara Higashinada-ku
Kobe-shi Hyogo-ken(JP)

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(22) Inventor: Ueda, Shuichi
213, Aza-Todoroki Yoshimari Ojin-cho
Tokushima-shi Tokushima-ken(JP)

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(22) Inventor: Ishida, Naobumi
1-163, Aza-Marusu Hiroshima Matsushige-cho
Itano-gun Tokushima-ken(JP)

(26) Applicant: TAIHO PHARMACEUTICAL COMPANY
LIMITED
2-9, Kanda Tsukasa-cho Chiyoda-ku
Tokyo 101(JP)

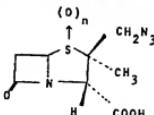
(22) Inventor: Ishizawa, Takeshi
41-15, Aza-Ejiriya Mitsuishi Naruto-cho
Naruto-shi Tokushima-ken(JP)

(27) Inventor: Micetich, Ronald G.
12, Braeside Terrace
Sherwood Park Alberta T-8A 3V-6(CA)

(22) Representative: Huskisson, Frank Mackie et al,
Fitzpatrick's 48 St. Vincent Street
Glasgow, G2 5TT Scotland(GB)

(28) Penicillin derivatives and process for preparation of the same.

(29) A penicillin derivative represented by the following formula, a pharmaceutically acceptable salt thereof and an ester thereof:



wherein n is 0, 1 or 2 and process for preparing the same.

EP 0 092 948 A2

PENICILLIN DERIVATIVES AND PROCESS
FOR PREPARATION OF THE SAME

This invention relates to penicillin derivatives
5 and pharmaceutically acceptable salts thereof and esters
thereof, and also to a process for preparing them.

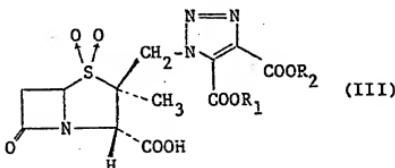
Of the commercially available antibiotics,
β-lactam type antibiotics having a β-lactam ring,
namely penicillins and cephalosporins, are best known
10 and frequently used. Although widely used as useful
chemotherapeutic drugs, the β-lactam type antibiotics
can not achieve satisfactory effects against some types
of microorganisms because of resistance of the micro-
organism to the β-lactam type antibiotics. The resistance
15 thereof are usually attributable to β-lactamase produced
by the microorganism. The β-lactamase is an enzyme which
acts to cleave the β-lactam ring of the β-lactam type
antibiotic, thereby causing the antibiotic to lose its
antimicrobial activity. For this reason, the action of
20 β-lactamase must be eliminated or inhibited so as to
enable the β-lactam type antibiotic to produce satis-
factory effects. The elimination or inhibition of the
β-lactamase activity can be achieved by β-lactamase
inhibitors, which are used conjointly with the β-lactam
25 type antibiotic to increase the antimicrobial activity

- 2 -

of the antibiotic.

It is an object of the present invention to provide novel compounds having β -lactamase inhibitory action.

- 5 It is another object of the invention to provide novel compounds useful as an intermediate for preparing the compounds having β -lactamase inhibitory action and represented by the formula



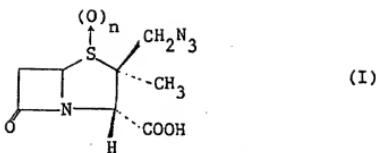
- 10 wherein R₁ and R₂ are lower alkyl group, respectively.

It is another object of the invention to provide processes for preparing the same.

- 15 It is a further object of the invention to provide a pharmaceutical composition having excellent β -lactamase inhibitory action.

It is an additional object of the invention to provide compositions which, when combined with β -lactam type antibiotics, can increase the antibacterial activity of the antibiotics.

- 20 The penicillin derivatives of the present invention are represented by the formula



wherein n is 0, 1 or 2.

The penicillin derivatives of the present invention, pharmaceutically acceptable salts thereof and esters thereof are all novel compounds and have β -lactamase inhibitory properties, hence useful as β -lactamase inhibitory agents.

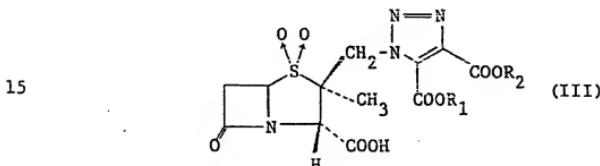
The penicillin derivatives of the invention, when used in combination with a known β -lactam type antibiotic, can increase the antimicrobial activity of the β -lactam type antibiotic.

Examples of antibiotics which can be used conjointly with the compounds of the present invention are β -lactam antibiotics which exhibit antibacterial action against gram-positive or gram-negative bacteria and which include commonly used penicillins such as ampicillin amoxicillin, hetacillin, ciclacillin, mecillinam, carbenicillin, sulbenicillin, ticarcillin, piperacillin, apalcillin, methicillin, mezlocillin and salts thereof; esters of penicillins such as bacampicillin, carindacillin, talampicillin, carfecillin and pivmecillinam; cephalosporins such as cephaloridine,

- 4 -

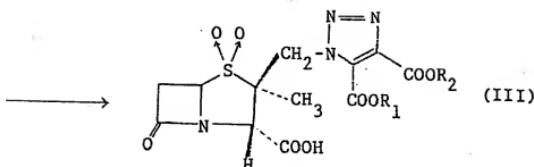
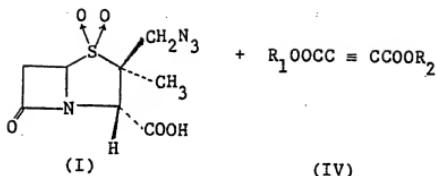
- cephalothin, cephapirin, cephacetrile, cefazolin,
cephalexin, cefradine, cefotiam, cefamandole, cefuroxime,
cefoxitin, cefmetazole, cefsulodin, cefoperazone,
cefotaxime, ceftizoxime, cefmenoxime, latamoxef,
5 cefaclor, cefroxadine, cefatrizine, cefadroxil,
cephaloglycin, and salts thereof. The β -lactam
antibiotic are usually used in an amount of about
0.1 to about 10 parts by weight, preferably about
0.2 to about 5 parts by weight, per part by weight
10 of the compound of the invention.

The derivatives of the present invention
are also useful as an intermediate for preparing the
compounds having β -lactamase inhibitory action and
represented by the formula



wherein R₁ and R₂ are lower alkyl group, respectively.

The compound of the formula (III) can be
prepared according to the reaction equation given below.



wherein R₁ and R₂ are as defined above. The process for preparing the compound of the formula (III) will be shown

5 in detail in reference examples to be described later.

Examples of the pharmaceutically acceptable salts of the derivatives having the formula (I) are salts of sodium, potassium, lithium or like alkali metals; salts of calcium, magnesium or like alkaline earth metals; salts of cyclohexylamine, trimethylamine diethanolamine or like organic amines; salts of alginine, lysine or like basic amino acids; ammonium salts; etc.

10 Examples of the esters of the present derivatives having the formula (I) include those which have carboxy protecting groups acceptable in the synthesis of the compounds of formula (III) and which are pharmaceutically

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acceptable. The term pharmaceutically acceptable ester refers to an ester which is easily hydrolyzed in vivo, the term ester to be hydrolyzed in vivo means a non-poisonous ester which rapidly decomposes in the blood or tissue of humans, producing the corresponding acid of the formula (I). Specific examples of the ester residues are methyl, ethyl, propyl, tert-butyl, pentyl, hexyl and like lower alkyl groups; methoxymethyl, ethoxymethyl, n-propyloxymethyl, iso-propyloxymethyl, 5 n-butoxymethyl, iso-butoxymethyl and like lower alkoxy-methyl groups; acetoxyethyl, propionyloxymethyl, n-butyryloxymethyl, iso-butyryloxymethyl, pivaloyloxy-methyl, 1-acetoxyethyl, 1-pivaloyloxyethyl, 1-pivaloyloxy-propyl, 1-propionyloxybutyl and like lower alkyl-10 carbonyloxy-lower alkyl; cyclopentylcarbonyloxyethyl, cyclohexylcarbonyloxyethyl and like (C_5-C_7 cycloalkyl)-carbonyloxy-lower alkyl groups; benzylcarbonyloxyethyl and like benzylcarbonyloxy-lower alkyl groups; benzoxyloxy-methyl, benzoxyloxyethyl and like benzoxyloxy-lower alkyl 15 groups, etc. The term "lower" used in conjunction with "alkyl" or "alkoxy" is intended to indicate that each alkyl or alkoxy portion therein can contain 1 to 6 carbon atoms. The alkyl or alkoxy groupings can be straight- or branched-chain groups. Other examples of 20 the penicillin carboxy protecting radicals include 3- 25

- 7 -

phthalidyl, crotonolacton-4-yl, γ -butyrolacton-4-yl and like lactones; iodomethyl, 2,2-dibormoethyl, 2,2,2-trichloroethyl and like halogenated lower alkyl groups substituted with 1 to 3 halogen atoms such as Cl, Br, I;

5 benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, diphenylmethyl and like methyl groups which may be unsubstituted or may be substituted with methoxy or nitro on the phenyl; tetrahydropyranyl, dimethylaminoethyl, dimethylchlorosilyl, trichlorosilyl; (2-oxo-1,3-dioxoden-4-yl)methyl, (5-methyl-2-oxo-1,3-dioxoden-4-yl)methyl, (5-phenyl-2-oxo-1,3-dioxoden-4-yl)methyl and like (5-substituted or unsubstituted-2-oxo-1,3-dioxoden-4-yl)-methyl groups, etc.

In the synthesis of penicillin compounds,

15 a material is esterified to protect penicillin carboxyl groups present in the material. Usable in the present invention as the ester-protecting groups are those heretofore used, i.e., those which are sufficiently stable in the reaction and which does not permit the

20 cleavage of the β -lactam ring in removal of the ester-protecting groups. Examples of such ester-protecting groups commonly used are methyl group substituted with 1 to 3 phenyl groups which may be unsubstituted or may be substituted with methoxy or nitro on the phenyl, and

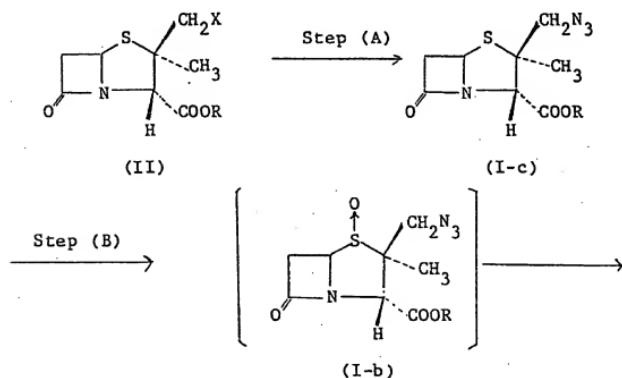
25 halogenated lower alkyl group.

- 8 -

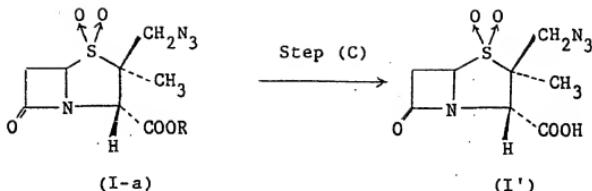
Examples of such pharmaceutically acceptable ester which can be hydrolyzed in vivo are lower alkyl carbonyloxy-lower alkyl, cycloalkyl (C_{5-7})-carbonyloxy-lower alkyl, benzylcarbonyl-lower alkyl-benzyloxy-lower alkyl, phthalidyl, lactones (5-substituted or unsubstituted-2-oxo-1,3-dioxoden-4-yl)methyl.

5 Examples of the present compound are:
 2β -azidomethyl-2 α -methylpenam-3 α -carboxylic acid-1,1-dioxide, 2β -azidomethyl-2 α -methylpenam-3 α -carboxylic
10 acid-1-oxide, and 2β -azidomethyl-2 α -methylpenam-3 α -carboxylic acid, and pharmaceutically acceptable salts thereof and esters thereof.

The penicillin derivatives of the present invention having the formula (I) can be prepared
15 according to the reaction scheme shown below:



- 9 -



In the foregoing formulae, X represents chlorine atom or bromine atom and R represents penicillin carboxy protecting group.

5 The penicillin carboxy protecting groups expressed by R are acceptable in the synthesis of the compounds of formula (III).

The steps (A), (B) and (C) of the foregoing process will be described below in detail.

10 Step (A)

A penicillanic acid derivative of the formula (II) is reacted with a metal azide to provide a compound of the formula (I-c). The reaction is conducted in a suitable solvent by reacting a known penicillanic acid derivative of the formula (II) with a metal azide in an amount of about 1 to about 50 moles, preferably about 1 to about 10 moles, per mole of the derivative of the formula (II). Examples of the metal azide which can be used include those commonly employed in the art such as sodium azide, potassium azide and like azides of alkali

- 10 -

metals, and barium azide and like azides of alkaline earth metals. The solvents useful in the reaction are not particularly limited and include any of those which do not affect the reaction, such as dimethylformamide, 5 ethyl acetate, acetone, dichloromethane, tetrahydrofuran, dioxane, methanol, ethanol and like organic solvents. These solvents are used singly or in mixture, and also can be employed as mixed with water. The reaction proceeds usually at a temperature between about -20 to 10 about 100°C, preferably about 0 to about 60°C. After completion of the reaction, the resulting product can be used in subsequent procedure without isolation or alternatively after isolation and purification by a conventional method.

15 Step (B)

The compound of the formula (I-c) obtained in step (A) is oxidized to sulfoxide of the formula (I-b) as an intermediate and eventually to dioxide of the formula (I-a). The oxidation is carried out by employing a 20 commonly used oxidizing agent such as permanganic acid, periodic acid, peracetic acid, performic acid, trifluoro peracetic acid, perbenzoic acid, m-chloro perbenzoic acid, hydrogen peroxide or the like. The oxidizing agent can be used in large excess, and may be employed 25 preferably in an amount of about 1 to about 2 moles per

mole of the compound of the formula (I-c). The reaction is usually carried out in a suitable solvent. Useful solvents include any of those which do not affect the reaction such as chloroform, pyridine, tetrahydrofuran, dioxane, methylene chloride, carbon tetrachloride, acetic acid, formic acid, dimethylformamide, etc.

The reaction temperature is not particularly limited, but the reaction is usually conducted at about -20 to about 50°C, preferably about 0 to about 30°C.

Depending upon the kind of the penicillin carboxy protecting group, the compounds of the formula (I-c) or (I-a) obtained in step (A) or (B) may be a pharmaceutically acceptable ester of the penicillin derivatives of the present invention having the formula (I) which can be hydrolyzed in vivo. However, if the compounds of the formulae (I-a) and (I-c) are not the contemplated pharmaceutically acceptable ester derivatives of the formula (I), the compounds of the formulae (I-c) or (I-a) are subjected to de-esterification as in step (C) to form a dioxide derivative of the formula (I') which, in turn, is converted in the conventional manner into a pharmaceutically acceptable salt or ester thereof which can be hydrolyzed in vivo. The esterification involved is carried out by a usual method. The compound of the formula (I-c) or (I-a) can be made into an ester

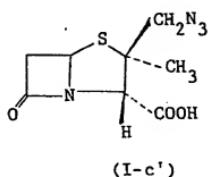
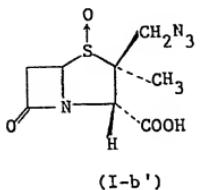
- 12 -

which can be hydrolyzed in vivo or a pharmaceutically acceptable salt thereof by the conventional ester interchange or salt-forming reaction.

Step (C)

5 The compound of the formula (I-a) is subjected to de-esterification without or after isolation from the reaction mixture obtained in step (B), whereby dioxide of the formula (I') is obtained.

10 Although not shown in the foregoing reaction scheme, following the general procedure of step (C) and using the compound of the formula (I-b) or (I-c) in place of the compound of the formula (I-a) as a starting material, there is provided the corresponding desired penicillin derivatives of the invention in the 15 form of free acid, i.e. the derivatives of the following formulae:



The de-esterification can also be carried out without or after isolating the starting materials of the formula (I-b) or (I-c) from the reaction mixture.

As the de-esterification method, reduction, hydrolysis, treatment with an acid and like method can be employed for converting the carboxy protecting group to carboxyl group. For example, if the carboxy protecting group is an active ester, the reaction frequently proceeds with ease under mild hydrolysis conditions or by merely bringing the ester into contact with water. The reduction method is employed when the carboxy protecting group is trichloroethylbenzyl, p-nitrobenzyl, diphenyl methyl or the like. Treatment with an acid is adopted when the carboxy protecting group is 4-methoxybenzyl, tert-butyl, trityl, diphenylmethyl, methoxymethyl, tetrahydropyranyl or the like.

The readduction can be conducted by treating the ester of the formula (I) with a mixture of (a) zinc, zinc-amalgam or like metal and/or chromium chloride, chromium acetate or like chromium salt and (b) formic acid, acetic acid or like acid. Alternatively, the reduction can be conducted with use of a catalyst in hydrogen atmosphere in a solvent. Examples of the catalysts are platinum, platinum oxide, palladium, palladium oxide, palladium-barium sulfate, palladium-calcium carbonate, palladium-carbon, nickel oxide, Raney-nickel, etc. The solvents are not particularly limited so far as they do not affect the reaction, and

- 14 -

include methanol, ethanol and like alcohols; tetrahydrofuran, dioxane and like ethers; ethyl acetate and like esters; acetic acid and like fatty acids; and a mixture of these organic solvents and water.

5 The acids useful for eliminating the carboxy protecting group of the ester of the formula (I) are formic acid, acetic acid and like lower fatty acids; trichloroacetic acid, trifluoroacetic acid and like trihalogenated acetic acids; hydrochloric acid, hydrofluoric acid and like hydrohalogenic acids; p-toluene-sulfonic acid, trifluoromethane-sulfonic acid and like organic sulfonic acids; and a mixture of these. In this reaction, when the acid used is in a liquid state and acts also as a solvent, it is not necessary 10 to use other solvents. However, dimethylformamide, dichloromethane, chloroform, tetrahydrofuran, acetone 15 and like solvents which do not affect the reaction may be used.

The penicillin derivative of the present
20 invention having the formula (I), i.e., the derivative of the formula (I') and the derivative in the form of free acid which corresponds to the starting compound of the formula (I-b) or (I-c), can be transformed by the salt-forming reaction or esterification commonly 25 employed in the art into a pharmaceutically acceptable

- 15 -

salt or ester which is hydrolyzed in vivo.

If the ester residue is, for example, 3-phthalidyl, crotonolacton-4-yl, γ -butyrolacton-4-yl or like group, the penicillin derivative of the formula 5 (I) can be alkylated by using 3-halogenated phthalide, 4-halogenated crotonolactone, 4-halogenated- γ -butyrolactone or the like. Suitable halogens of the foregoing halides include chlorine, bromine, iodine, etc. The reaction is carried out by dissolving the 10 salt of the penicillin derivative of the formula (I) in N,N-dimethylformamide or like suitable polar organic solvent and adding an approximately equimolecular amount of a halide to the solution. The reaction temperature ranges from about 0 to about 100°C, preferably from 15 about 15 to about 35°C. Suitable salts of the penicillin derivative to be used in the esterification are salts of sodium, potassium or like alkali metals; salts of triethylamine, ethyldiisopropylamine, N-ethylpiperidine, N,N-dimethylaniline, N-methylmorpholine or like tertiary 20 amines, etc. After completion of the reaction, the contemplated product can be easily separated by the conventional method and also can be purified, when required, by recrystallization, thin layer chromatography, column chromatography or like method.

25 The penicillanic acid derivative of the present

invention, a pharmaceutically acceptable salt thereof and ester thereof which is hydrolyzed in vivo are mixed with a suitable antibiotic substance to form a preparation which is orally or parenterally administered.

- 5 Alternatively, the present compound and a suitable antibiotic can be separately administered. Thus the derivatives of the formula (I) can be used for treating infections disease of human beings and other animals.

The composition of the present invention may 10 be made into tablets, pills, capsules, granules, powders, syrups, lozenges, solutions, suspensions, etc. for oral administration and aqueous, suspending or water-soluble preparations for intravenous, subcutaneous or intramuscular injections.

- 15 Carriers useful in formulating the preparations are those commonly used pharmaceutically acceptable non-toxic carriers such as gelatin, lactose, starch, magnesium stearate, talc, vegetable oil, animal oil, polyalkylene glycol, etc. The carrier may be used with other additives 20 such as diluents, binders, buffer agents, preservatives, glazes, disintegrators, coating agents, etc.

The daily dose of the preparation can be appropriately determined and is not particularly limited. Preferably the daily dose is such that the total amount 25 of the present compound and β -lactam antibiotic is about

- 17 -

1 to about 200 mg/Kg body weight for oral administration and about 1 to about 100 mg/Kg body weight for parenteral administration.

The present invention will be described below
5 in more detail with reference to examples given below.

Example 1

Preparation of benzhydryl 2β-azidomethyl-2α-methylpenam-3α-carboxylate

An aqueous solution of 2.38 g of sodium azide
10 and 25 ml of water was added to a solution of benzhydryl 2β-chloromethyl-2α-methylpenam-3α-carboxylate (2.44 g) in dimethylformamide (100 ml). The mixture was stirred at room temperature for 4 hours. The resulting reaction mixture was poured into water and the mixture was
15 extracted with ether. The ether layer was washed with water and concentrated to provide 2.2 g of the contemplated product as oil in 89 % yield.

Infrared absorption spectrum (nujol)

ν max (cm^{-1}): 2120, 1812, 1765

20 Nuclear magnetic resonance spectrum (CDCl_3)

δ (ppm) : 1.30 (3H, s), 3.25 (2H, m),
3.42 (1H, d), 3.63 (1H, d),
4.75 (1H, s), 4.76 (1H, m),
7.00 (1H, s), 7.40 (10H, s)

- 18 -

Example 2

Preparation of benzhydryl 2 β -azidomethyl-2 α -methylpenam-3 α -carboxylate

- An aqueous solution of 2.38 g of sodium azide
5 and 25 ml of water was added to a solution of benzhydryl
2 β -bromomethyl-2 α -methylpenam-3 α -carboxylate (2.71 g)
in acetone (100 ml). The mixture was stirred at room
temperature for 5 hours. The acetone was removed by
distillation and the residue was extracted with ether.
10 The extract was concentrated to provide 2.15 g of the
contemplated product as oil in 86 % yield.

The infrared absorption spectrum and nuclear
magnetic resonance spectrum of the product obtained
above were identical with those of the product prepared
15 in Example 1.

Example 3

Preparation of benzhydryl 2 β -azidomethyl-2 α -methylpenam-3 α -carboxylate 1,1-dioxide

- To a solution of benzhydryl 2 β -azidomethyl-
20 2 α -methylpenam-3 α -carboxylate (2.22 g) in a mixture
of acetic acid (75 ml) and water (12 ml) was added
potassium permanganate (1.9 g). The mixture was
stirred at room temperature for 4 hours. The excess
potassium permanganate was destroyed by 30 % hydrogen
25 peroxide and the reaction mixture diluted with excess

- 19 -

ice water. The precipitate was collected by filtration, and washed with water. The resulting product was dissolved in ether and the ether extract was washed with an aqueous solution of sodium bicarbonate and brine.

- 5 Concentration gave 1.49 g of the contemplated product in 62.2 % yield.

Infrared absorption spectrum (nujol)

ν_{max} (cm^{-1}): 2120, 1812, 1765

Nuclear magnetic resonance spectrum (CDCl_3)

- 10 δ (ppm) : 1.18 (3H, s), 3.50 (2H, d),
3.72 (1H, d), 3.93 (1H, d),
4.60 (1H, m), 4.65 (1H, s),
7.00 (1H, s), 7.36 (10H, s)

Example 4

- 15 Preparation of sodium 2*B*-azidomethyl-2*a*-methylpenam-3*a*-carboxylate-1,1-dioxide

- A 100 mg quantity of benzhydryl 2*B*-azidomethyl-2*a*-methylpenam-3*a*-carboxylate-1,1-dioxide was dissolved in a mixture of 50 ml of tetrahydrofuran and 50 ml of
20 water and 50 mg of 10 % palladium charcoal was added. The mixture was hydrogenated at room temperature under a pressure of 1 kg/cm^2 . After absorption of the hydrogen was completed, the reaction mixture was filtered and the tetrahydrofuran was removed from the filtrate by
25 distillation. To the residue was added 19.1 mg of

- 20 -

sodium bicarbonate. The aqueous mixture was washed with chloroform and was chromatographed with a column of high porous polymer and eluted with water-10 % acetone in water (gradient). The liquid thus obtained was freeze-dried to afford 21 mg of sodium 2 β -azidomethyl-2 α -methylpenam-3 α -carboxylate as white powder in 37.3 % yield.

Infrared absorption spectrum (KBr)

ν max (cm^{-1}): 2140, 1785, 1630

Nuclear magnetic resonance spectrum (D_2O)

10 δ (ppm) : 1.51 (3H, s), 3.36 (1H, dd),
 3.64 (1H, dd), 4.00 (2H, s),
 4.27 (1H, s), 4.95 (1H, dd)

Example 5

Preparation of potassium 2 β -azidomethyl-2 α -methylpenam-15 3 α -carboxylate-1,1-dioxide

Benzhydryl 2 β -azidomethyl-2 α -methylpenam-3 α -carboxylate-1,1-dioxide (110 mg) was dissolved in 2 ml of formic acid. The solution was left to stand for 10 minutes and freeze-dried. The residue was dissolved 20 in a buffer solution of phosphoric acid (0.2 M) with its pH adjusted to 7.2 using potassium phosphate monobasic and potassium phosphate dibasic. The aqueous mixture was washed with chloroform and was chromatographed with a column of high porous polymer and eluted 25 with water-10 % acetone in water (gradient). The liquid

thus obtained was freeze-dried to provide 25 mg of potassium salt of 2 β -azido-2 α -methylpenam-3 α -carboxylate as white powder in 37.9 % yield.

Infrared absorption spectrum (KBr)

5 ν max (cm^{-1}): 2140, 1785, 1630

Nuclear magnetic resonance spectrum (D_2O)

δ (ppm) : 1.52 (3H, s), 3.37 (1H, dd),
 3.65 (1H, dd), 4.02 (2H, s),
 4.29 (1H, s), 4.96 (1H, dd)

10 The compounds of the present invention obtained above were checked for pharmacological activity in the following manner.

(1) β -lactamase inhibitory activity

15 The compounds of the present invention obtained in the examples were tested by pH Stat method (Journal of Pharmaceutical Science, Vol. 61, No.10, pp 1954 to 1958, published in 1972) for inhibitory activity against penicillinase (β -lactamase) from *Bacillus* SP.

20 The test results revealed that the sodium 2 β -azidomethyl-2 α -methylpenam-3 α -carboxylate-1,1-dioxide had a 50 % β -lactamase inhibitory concentration (IC_{30}) of $4 \times 10^{-6}\text{M}$. The other derivatives obtained in the other examples were found to have similar values in IC_{50} .

(2) Antibacterial activity (synergistic effects

25 attainable by the combined use of the present compounds and ampicillin or mecillinam)

The compounds of the present invention, ampicillin and mecillinam, each singly used, were checked for minimal inhibitory concentration (MIC) against the bacteria listed in Table 1 given below by 5 the standard method of Japan Society of Chemotherapy (Chemotherapy, Vol. 29, No.1 p76 to 79). The MICs of ampicillin or mecillinam as combined with the present compounds (10 g/ml) were also measured, against the same bacteria. Mueller Hinton Broth (Difco) was used 10 as the growth medium and Mueller Hinton Agar (Difco) as the medium measuring the MIC. Table 1 below shows the results.

The bacteria used in the tests are those heretofore known and preserved in a depository, and 15 are all offered by Dr. Nishino at Department of Microbiology, Kyoto College of Pharmacy except P. Vulgaris.

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- 23 -

Table 1

Test Bacteria	Amount of Inoculum size (cell/ml)	MIC (kg/ml)			
		Test of Ampicillin and/or Compound of Example 4	Test of Mecillinam and/or Compound of Example 4	Mecillinam Compound of Ex. 4	Combined Use of Ampicillin and Comp. of Ex. 4. (10 μ g/ml)
S. aureus S-54	10 ⁸	100	>100	0.2	800
S. aureus No. 80	10 ⁸	100	>100	0.2	800
E. coli No. 21	10 ⁸	-	-	-	>800
P. mirabilis 121-1	10 ⁶	200	50	6.25	-
P. vulgaris IID OX-19	10 ⁸	-	-	-	400
					25
					3.13

- 24 -

Example 6

Preparation of p-nitrobenzyl 2β-azidomethyl-2α-methylpenam-3α-carboxylate

The procedure of Example 1 was repeated
5 with the exception of using as the starting material
p-nitrobenzyl 2β-chloromethyl-2α-methylpenam-3α-carboxylate, affording the above contemplated compound.

Infrared absorption spectrum (KBr)

ν_{max} (cm⁻¹): 2120, 1798, 1760

10 Nuclear magnetic resonance spectrum (CDCl₃)

δ (ppm) : 1.40 (3H, s), 3.12 (1H, dd),
3.50 (2H, s), 3.62 (1H, dd),
4.83 (1H, s), 5.29 (2H, s),
5.36 (1H, dd), 7.56 (2H, d),
15 8.26 (2H, d)

Example 7

Preparation of p-nitrobenzyl 2β-azidomethyl-2α-methylpenam-3α-carboxylate-1,1-dioxide

The procedure of Example 3 was followed
20 with the exception of using as the starting material
p-nitrobenzyl 2β-azidomethyl-2α-methylpenam-3α-carboxylate, giving the above contemplated compound.

Infrared absorption spectrum (KBr)

ν_{max} (cm⁻¹): 2120, 1770

- 25 -

Nuclear magnetic resonance spectrum (CDCl_3)

δ (ppm) : 1.42 (3H, s), 3.45-3.60 (2H, m),
3.75 (1H, d), 3.96 (1H, d),
4.56-4.75 (1H, m), 4.64 (1H, s),
5.33 (2H, s), 7.56 (2H, d),
8.26 (2H, d)

Reference Example 1

Preparation of benzhydryl 2 β -(4,5-dimethoxy-carbonyl-1,2,3-triazol-1-yl)methyl-2 α -methylpenam-3 α -carboxylate-1,1-dioxide

A mixture of 0.870 g of benzhydryl 2 β -azido-methyl-2 α -methylpenam 3 α -carboxylate-1,1-dioxide and 0.618 g of dimethylacetylene-dicarboxylate was stirred in 15 ml of benzene with reflux in nitrogen atmosphere for 18 hours. The solvent was removed by distillation. The residue was chromatographed on silica gel column with ethyl acetate-chloroform (1:3) as eluate, giving 0.495 g of the contemplated product as light yellow crystals in 44 % yield which melts at 75 to 77°C.

20 Infrared absorption spectrum (KBr)

ν_{max} (cm^{-1}): 1800, 1735

- 26 -

Nuclear magnetic resonance spectrum (CDCl_3)

5 δ (ppm) : 1.20 (3H, s), 3.48 (2H, t),
 3.97 (3H, s), 3.98 (3H, s),
 4.59 (1H, m), 4.95 (1H, s),
 5.26 (2H, s), 6.97 (1H, s),
 7.36 (10H, s)

Reference Example 2

Preparation of sodium 2α -(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)methyl-2 α -methylpenam-3 α -carboxylate-

10 1,1-dioxide

Hydrogenation was conducted at ordinary pressure and room temperature by using 100 ml of tetrahydrofuran, 100 ml of water, 116 mg of benzhydryl 2β -(4,5-dimethoxycarbonyl-1,2,3-triazol-1-yl)-methyl-15 2 α -methylpenam-3 α -carboxylate-1,1-dioxide, 58 mg of 10 % palladium charcoal and 17 mg of sodium bicarbonate. After the absorption of the hydrogen was completed, the reaction mixture was filtered and the tetrahydrofuran was removed from the filtrate at reduced pressure by 20 distillation. The residue was washed with chloroform and the aqueous solution was concentrated at reduced pressure. The aqueous mixture was washed with chloroform and was chromatographed with a column of high porous polymer and eluted with water-10 % acetone in water 25 (gradient). The liquid thus obtained was freeze-dried

- 27 -

to obtain 53 mg of the contemplated product as white powder in 60 % yield. The white powder decomposed at over 165°C.

Infrared absorption spectrum (KBr)

5 ν max (cm^{-1}): 1785, 1735, 1630

Nuclear magnetic resonance spectrum (D_2O)

δ (ppm) : 1.41 (3H, s), 3.40 (1H, dd),
 3.80 (1H, dd), 3.98 (3H, s),
 4.05 (3H, s), 4.51 (1H, s)
10 5.03 (1H, dd), 5.48 (2H, d)

Given below are examples of preparation of the present antibacterial compositions.

Preparation Example 1

	Ampicillin	200 mg
15	Compound of Example 4	200 mg
	Lactose	100 mg
	Crystalline cellulose	57 mg
	<u>Magnesium stearate</u>	<u>3 mg</u>
20	Total	560 mg
		(amount per capsule)

The above ingredients are formulated in the proportions listed above into a capsule.

- 28 -

Preparation Example 2

	Amoxycillin	100 mg
	Compound of Example 5	70 mg
	Lactose	330 mg
5	Corn starch	490 mg
	<u>Hydroxypropyl methyl cellulose</u>	10 mg
	Total	1000 mg

(amount per dose)

The above ingredients are formulated in the
10 proportions listed above into granules.

Preparation Example 3

	Pivmecillinam	70 mg
	Compound of Example 4	70 mg
	Lactose	33 mg
15	Crystalline cellulose	15 mg
	Magnesium stearate	3 mg
	Talc	4 mg
	Corn starch	15 mg
	<u>Hydroxypropyl methyl cellulose</u>	10 mg
20	Total	220 mg

(amount per tablet)

The above ingredients are formulated in the
proportions listed above into a tablet.

- 29 -

Preparation Example 4

Compound of Example 5	120 mg
Hydroxypropyl cellulose	3 mg
Corn starch	25 mg
<u>Magnesium stearate</u>	<u>2 mg</u>
Total	150 mg

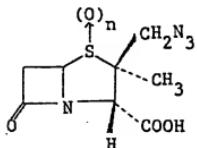
(amount per tablet)

The above ingredients are formulated in the proportions listed above into a tablet.

CLAIMS:

1. A penicillin derivative represented by the following formula, a pharmaceutically acceptable salt thereof and an ester thereof:

5

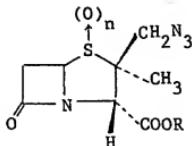


wherein n is 0, 1 or 2.

2. A pharmaceutically acceptable salt of the derivative as defined in claim 1 which salt is an alkali metal salt, alkaline earth metal salt, ammonium salt, organic amine salt and basic amino acid salt.

10 3. An ester of the derivative as defined in claim 1 in which the ester is pharmaceutically acceptable and can be hydrolyzed in vivo, and is represented by the formula:

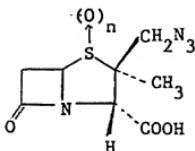
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wherein R represents pharmaceutically acceptable ester residue and n is as defined above.

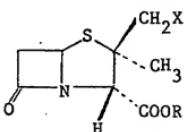
4. A process for preparing a penicillin

derivative of the following formula and pharmaceutically acceptable salt thereof and an ester thereof:



wherein n is as defined above, the process comprising

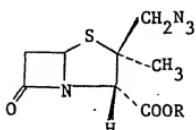
- 5 the steps of reacting a compound of the formula



wherein X represents chlorine atom or bromine atom,
and R and n are as defined above, with a metal azide
and, when required, carrying out any of oxidation,

- 10 de-esterification, ester interchange and salt-forming
reaction.

5. A process as defined in claim 4 in which
a compound of the formula

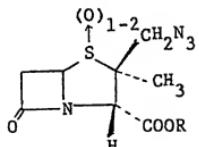


- 15 wherein R is as defined above is prepared without

resorting to oxidation after completion of the reaction with the metal azide.

6. A process as defined in claim 4 in which
a compound of the formula

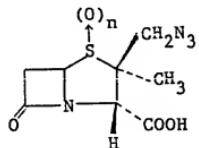
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wherein R is as defined above is prepared by carrying out oxidation after completion of the reaction with the metal azide.

7. A process as defined in claim 6 in which
10 a compound of the formula

10



wherein n is 0, 1 or 2 is prepared by carrying out de-esterification subsequent to or without oxidation after completion of the reaction with the metal azide.

- 15 8. A process as defined in claim 4 in which a salt of the penicillin derivative is prepared by effecting salt-forming reaction subsequent to or without oxidation after completion of the reaction with the metal azide.



European Patent
Office

EUROPEAN SEARCH REPORT

0092948

Application number

EP 83 30 2160

DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	EP-A-0 013 067 (BEECHAM) * Claims 1,4 *	1
A	EP-A-0 008 917 (PFIZER) * Claims 1-4 *	1

TECHNICAL FIELDS SEARCHED (Int. Cl.?)		
C 07 D 499/00 A 61 K 31/43		
C 07 D 499/00 A 61 K 31/00		
The present search report has been drawn up for all claims		
Place of search THE HAGUE	Date of completion of the search 26-08-1983	Examiner CHOULY J.
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone	T : theory or principle underlying the invention	
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